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Synthesis of Non-centrosymmetric Dipolar 4,4′-Bipyridines: Potential Molecular Tectons for Programmed Assembly of Supramolecular Systems

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In this report, we describe a modular synthesis approach towards a new series of non-centrosymmetric, dipolar 4,4′-bipyridines bearing 2,6- and 3,5-functionalized pyridyl moieties at the peripheries. Central to our strategy is the selective substitution on only one pyridyl motif that could contain electron-donating (–CH_3) or electron-withdrawing (–F, –Cl, –CF_3) groups which causes electronic/steric effects on one nitrogen atom in 4,4′-bipyridines. This synthetic protocol was further applied to prepare azo-functionalized (–N=N–) asymmetric bipyridines and non-centrosymmetric 4,4′-bipyridine *N*-oxide scaffolds, which overcome the synthetic hurdles oxidizing 4,4′-bipyridines to *N*-monoxides selectively at only one pyridine. Compared to the conventional symmetrical bipyridines, the dipolar non-centrosymmetric molecular tectons pave the way for the realization of non-centrosymmetric supramolecular assemblies because of the difference in the binding energy of the pyridyl nitrogen atoms.

Introduction

Bipyridyl-based molecular tectons, the most widely used nitrogen-containing aromatic heterocyclic scaffolds, have been largely investigated as nitrogen-donor ditopic ligands to generate diverse supramolecular assemblies with tailored architectures and functions.[1] To form a non-covalent supramolecular assembly, the building block design (size, shape, geometry, and directionality) as well as controlling forces that hold molecular tectons together either (through coordination-driven approaches, or supramolecular interactions of π-π stacking or hydrogen bonds), are of utmost relevance that provides precise control over the molecular assembly.[2] Designing function-inspired diverse classes of molecular tectons, we have previously synthesized some of the most prevalent molecular components with different sizes/lengths (by including benzene rings as spacer groups),[3] which are suitable for developing crystalline porous coordination assemblies.[4] Incorporating distinct functional features into such molecular tectons, for instance, stereochemistry,[5] switchability, photo-tunability or stimuli-responsiveness,[6] thus being applicable for dynamic photo-, and mechanochemical control has tremendous potential from diverse applications perspective because such molecular features could be inherited once assembled into materials.[7] Beyond the concept of porous coordination assemblies, we have demonstrated the formation of halogen-bonded supramolecular assemblies co-crystallized with mono-, di-, and triiodofluorobenzenes, where molecular geometry of the bipyridines and halogen-bond directionality translates into the corresponding co-crystal assembly.[8] Employing bipyridines, the co-crystal assembly approach to obtain supramolecular stacking through intermolecular hydrogen bonding in solid-state has also been demonstrated.[9] In these studies, most often symmetrical 4,4′-bipyridines were used,[10] while material synthesis using asymmetric bipyridines is much less common in literature. We have a special interest in exploring materials with non-centrosymmetric structures which show an assortment of interesting properties such as second harmonic generation (SHG), piezoelectric or ferroelectric properties.[11] To achieve this objective and to avoid the center symmetry trap when assembling dipolar building blocks, the structural and functional design of the linear non-centrosymmetric dipoles is a prerequisite of the materials with a static electric field. In this context, herein we report the modular synthesis of a new series of non-centrosymmetric 4,4′-bipyridines with various functional moieties attached at the 2,6 and 3,5 positions of the pyridyl core for the realization of programmed directional self-assembly.

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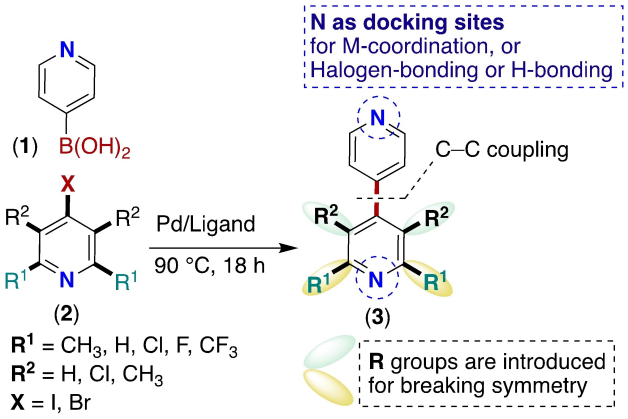
Results and Discussion

The synthesis was focused on grafting various substituents selectively on only one pyridine ring that could contain electron-donating (–CH_3) or electron-withdrawing (–F, –Cl, –CF_3) groups. Due to the altered electron distribution within only one pyridine ring, either an increased or a decreased basicity of the nitrogen atom can be achieved. We aimed at the synthesis of functionalized 4,4′-bipyridines with varying substitution patterns employing the preeminent Pd-catalyzed stepwise borylation/Suzuki-Miyaura reaction for the construction of the aryl-aryl bonds (Scheme 1).

After careful optimization of the reaction parameters, including palladium source/ligand, and solvent effects (1,4-dioxane/water), using tris(dibenzylidenacetone)dipalladium chloroform complex [$Pd_2(dba)_3 \cdot CHCl_3$] as the catalyst and tricyclohexylphosphane as ligand proved to be important to obtain the corresponding coupling products in high yield. The reactions were carried out at a temperature of 90–110 °C for 18 hours and afforded the differently functionalized non-centrosymmetric dipolar 4,4′-bipyridines in good overall yields (from 46 to 94%) employing a range of mono- and disubstituted methyl-, chloro-, and fluoro-pyridines as precursor components in combination with 4-pyridyl-derived organoboranes.



Scheme 1. Modular approach for the synthesis of differently functionalized non-centrosymmetric dipolar 4,4′-bipyridine tectons.

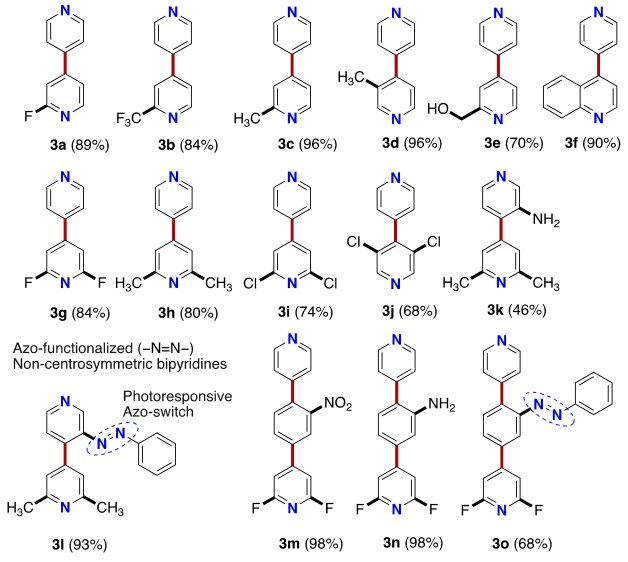
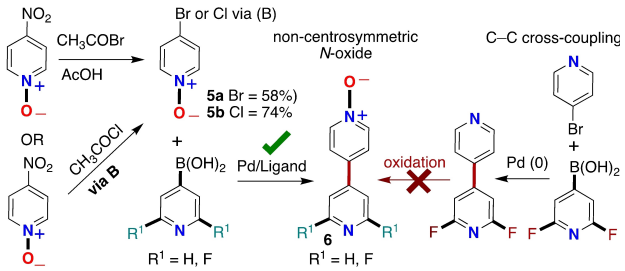


Figure 1. Differently functionalized non-centrosymmetric dipolar 4,4′-bipyridines tectons (**3a-o**) prepared via Pd-catalyzed Suzuki-Miyaura and Mill reaction.

Different R groups, including methyl-, chloro-, and fluoro-substitutions selectively at only one pyridine motif, were aimed to break molecular symmetry and render a dipole moment to the product resulting from different electronic effects on the nitrogen atoms within 4,4′-bipyridines (**3a–j**). When trying to couple 4-pyridylboronic acid and 3,5-dichloro-4-iodopyridine, we obtained the product (**3j**) in low yield (Figure 1). Defluorination was observed when applying harsh conditions at high temperatures. The synthesis route to achieve non-centrosymmetric 4,4′-bipyridine tectons bearing electron-donating (–CH_3) groups on one pyridyl motif and electron-withdrawing (–F) group on the other pyridyl which would cause enhanced electronic effects remained unsuccessful.

This modular strategy was extended for synthesizing azo-functionalized asymmetric bipyridines (**3l,3o**) by using stepwise Mills/Suzuki-Miyaura cross-coupling reactions, which involve an aromatic amine and a nitrosoarene to form the azobenzene moiety (see the ESI for details).[12] After integrating azo-functionalized tectons into complex systems, the azobenzene core –N=N– grafted to the molecular backbone can be transformed reversibly on irradiation, which imparts photosensitivity and allows photo-controlled smart functions.[13]

This synthetic protocol was also deployed to prepare non-centrosymmetric 4,4′-bipyridine *N*-oxide scaffolds (**6a–c**) by introducing bromo-, and chloropyridine *N*-oxides (**5a,b**) as coupling components in the Suzuki-Miyaura cross-coupling. 4-Nitropyridine *N*-oxide can be transformed into a 4-halopyridine *N*-oxide via a nucleophilic substitution reaction (Scheme 2). 4-chloropyridine *N*-oxide could be obtained in a 74% yield when the nitropyridine was stirred using an excess of acetyl chloride (26 equiv.) for 30 minutes at 50 °C. 4-bromopyridine *N*-oxide could not be synthesized under similar conditions using 48% hydrobromic acid. However, when the reaction was repeated with the use of acetyl bromide instead of hydrobromic acid, it was possible to isolate the target product in 58% yield. 74% of 4-bromopyridine *N*-oxide was obtained using 15 equiv. of acetyl bromide in acetic acid. This approach thus enables us to



Scheme 2. Modular synthesis of non-centrosymmetric *N*-oxides via cross-coupling of halopyridine *N*-oxides in Suzuki-Miyaura reaction.

overcome the synthetic hurdles in oxidizing 4,4′-bipyridine selectively to the *N*-monoxide at only one of the pyridine units, as the first *N*-oxidation is not selective.[14] Oxidation of 2,6-difluoro-4,4′-bipyridine *N*-oxide employing the traditional route was not successful.

Ensuing the holistic approach of functional molecules for functional materials – by installing the 4-pyridyl moieties at the peripheries of the tectons enables to form coordination networks with metal ions/clusters or non-coordination supramolecular assemblies via intermolecular interactions of halogen-bonding or hydrogen bonds. Both pyridines at the peripheries can serve as docking sites, which may either pack in parallel or antiparallel fashion depending on the interplay of subtle forces. Symmetric tectons would lead to a non-directional assembly and thus will be non-polar by nature. While non-centrosymmetric packing could be obtained by non-symmetrical polar molecular tectons. This strategy has been proven to be operational in the crystalline phase. For instance, the formation of 1–D directional coordination networks based on a 4,4′-bipyridines bearing two thioether groups of PySMe or $PyN(Me_2)_2$ moieties,[15] and noncentric packing of 1-D coordination networks based on non-centrosymmetric 4,4′-bipyridines bearing optically active two oxazoline units have been previously demonstrated.[16] This approach towards directional packing of coordination networks at the solid/liquid interface on graphite surfaces has also been realized.[17] In our preliminary research, as proof-of-concept, the useful utility of model dipolar asymmetric-bipyridines precursors, namely, 2,6-dimethyl-4,4′-bipyridine was demonstrated to form porous crystalline thin films using programmed layer-by-layer (lbl) assembly.[18] The lbl technique allowed for the quasi-epitaxial stacking of asymmetric dipolar 4,4′-bipyridine tectons to yield porous, crystalline molecular materials that lack inversion symmetry and contain a built-in electric field. The substitution-induced charge redistribution within the tectons results from the inductive effect of the functionalization groups. The dipolar 2,6-dimethyl-4,4′-bipyridine tecton exhibits a sizeable dipole moment directed towards the substituted ring with a calculated value of 1.0 D, and the non-centrosymmetric nature of the fabricated assembly is also evidenced by the presence of a substantial SHG signal. However, some further improvements are needed to achieve higher alignment ratios by screening optimal molecular tectons and optimizing the fabrication strategies. We conjuncture that through adding an additional element of chirality together with modulating steric and electronic effects within the non-centrosymmetric tectons could provide enhanced control over directionality and polarization. Moreover, intermolecular interactions (e.g., π-π stacking) could also assist to hold the molecular tectons in a particular conformational/directional alignment in programmed assemblies within which all non-centrosymmetric tectons are aligned in the same direction and hence has additional polarization. In this vein, investigations on the diverse library of dipolar tectons, aided by computer-aided design strategies, to engineer molecular materials exhibiting tailored architectures and functions are currently underway.

Conclusions

We have developed a modular synthesis approach to provide a broad set of structurally diverse, asymmetric 4,4′-bipyridines with an electric dipole. The 2,6- and 3,5-functionalized pyridyl moieties were synthesized using Pd-catalyzed cross-coupling reactions involving the aromatic organoboranes and appropriate 4-pyridylhalides. Central to our strategy is the selective substitution of only one pyridyl motif that could contain electron-donating or electron-withdrawing groups, which causes electronic effects on the nitrogen atoms within 4,4′-bipyridines. Compared to the conventional symmetrical 4,4′-bipyridines, stacking asymmetric dipolar tectons enables the fabrication of molecular materials that lack inversion symmetry and could be used for the engineering of functional materials with non-linear optical properties. As demonstrated in a proof-of-principle study, stacking of the non-centrosymmetric dipolar units by layer-by-layer techniques allows for the realization of molecular materials lacking inversion symmetry and with built-in electric fields.

Experimental Section

General methods. All substrates, reagents, and solvents employed here were commercially available and used as supplied without further purification. Thin-layer chromatography (TLC) was carried out on silica gel plates (Silica gel 60, F254, Merck) with detection by UV. Purifications were performed with preparative chromatography using normal-phase silica gel (Silica gel 60, 230–400 mesh, Merck). The compounds were characterized with nuclear magnetic resonance spectroscopy (NMR), high-resolution mass spectrometry (HRMS), and infrared spectroscopy (IR). NMR spectra were recorded on a Bruker Avance 400 NMR instrument at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR, or a Bruker Avance 500 NMR instrument at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR. The NMR spectra were recorded at room temperature in deuterated solvents. The chemical shift δ is displayed in parts per million [ppm] and the references used were the ^{1}H and ^{13}C peaks of the solvents themselves: d_1-chloroform ($CDCl_3$): 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C; d_6-dimethyl sulfoxide (DMSO-d_6): 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C; d_2-methylene chloride (CD_2Cl_2): 5.32 ppm for ^{1}H and 53.84 ppm for ^{13}C. For the characterization of centrosymmetric signals, the signal's median point was chosen for multiplets in the signal range. The following abbreviations were used to describe the proton splitting pattern: d = doublet, t = triplet, m = multiplet, dd = doublet of a doublet. Absolute values of the coupling constants *"J"* are given in Hertz [Hz] in absolute value and decreasing order. Signals of the ^{13}C spectra were assigned by phase-edited heteronuclear single quantum coherence (HSQC). Electron ionization (EI) experiments were conducted using a Finnigan, MAT 90 (70 eV) instrument, with 3-nitrobenzyl alcohol (3-NBA) as matrix and reference for high resolution. For the interpretation of the spectra, molecular peaks $[M]^+$, peaks of protonated molecules $[M+H]^{+,}$ and characteristic fragment peaks are indicated with their mass-to-charge ratio (*m/z*), and their intensity in percent, relative to the base peak (100%) is given. The infrared spectra were recorded with a Bruker Alpha P instrument. All samples were measured by attenuated total reflection (ATR). The positions of the absorption bands are given in wavenumbers $\tilde{\nu}$ in cm^{-1}.

General synthetic procedure for Suzuki-Miyaura cross-coupling reaction (GP): boronic acid (1 equiv.), iodo or bromo derivative of pyridines (1–5 equiv.), [1,1′-tris(dibenzylidenaceton)dipalladium chloroform complex [$Pd_2(dba)_3 \cdot CHCl_3$] as the catalyst source (5 mol%) and tricyclohexylphosphane as the ligand (5 mol%), and potassium phosphate (2 equiv.) as a base were added in a degassed dioxane/water mixture (2/1) under argon atmosphere. The mixture was refluxed at 90–110 °C temperature for 16 h to 19 h. The reaction mixture was cooled down to room temperature, then added water before being extracted with dichloromethane. Combined organic layers were washed with water and brine, then dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) to give the corresponding coupling product.

2-Fluoro-4,4′-bipyridine (3 a): Following the GP, 2-fluoro-4-iodopyridine (1.11 g, 5.00 mmol, 1.00 equiv.), 4-pyridylboronic acid (738 mg, 6.00 mmol, 1.20 equiv.), tris(dibenzylidenaceton)dipalladium chloroform (25.9 mg, 25.0 µmol, 0.00500 equiv.), tricyclohexylphosphane (16.8 mg, 60.0 µmol, 0.0120 equiv.) and potassium phosphate (2.12 g, 10.0 mmol, 2.00 equiv) were combined with a degassed mixture of 1,4-dioxane (12.0 mL) and water (5.00 mL). After stirring for 16 h at 110 °C, the mixture was cooled to 21 °C, extracted with ethyl acetate, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 5% MeOH to yield the title compound (779 mg, 4.47 mmol, 89% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.79–8.73 (m, 2H), 8.35 (d, J_{HH} = 5.3 Hz, 1H), 7.55–7.49 (m, 2H), 7.43 (ddd, J_{HH} = 5.2, 1.7, J_{HF} = 1.7 Hz, 1H), 7.19–7.14 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 164.7 (d, $^1J_{CF}$ = 239.4 Hz), 151.4 (d, $^3J_{CF}$ = 8.0 Hz), 151.0 (2 C), 148.8 (d, $^3J_{CF}$ = 15.3 Hz), 144.5 (d, $^4J_{CF}$ = 3.3 Hz), 121.5 (2 C), 119.5 (d, $^4J_{CF}$ = 4.2 Hz), 107.6 (d, $^2J_{CF}$ = 38.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = -66.8 (2-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3070 (w), 3044 (w), 3023 (w), 2965 (w), 2945 (w), 2927 (w), 2887 (w), 2863 (w), 1619 (w), 1609 (w), 1596 (vs), 1574 (w), 1537 (m), 1475 (m), 1417 (w), 1398 (vs), 1346 (w), 1336 (w), 1317 (m), 1289 (w), 1247 (w), 1221 (w), 1200 (s), 1126 (w), 1096 (w), 1078 (w), 1058 (w), 990 (m), 966 (w), 894 (s), 857 (m), 815 (vs), 737 (m), 667 (w), 640 (w), 616 (vs), 558 (s), 535 (vs), 497 (w), 482 (w), 469 (w), 439 (vs), 381 (w). MS (EI, 70 eV), m/z (%): 293 (17), 281 (29), 262 (34), 243 (28), 231 (31), 181 (58), 175 (11) $[M+H]^+$, 174 (100) $[M]^+$, 173 (25), 162 (5), 147 (8), 134 (6), 131 (14), 121 (6). HRMS (EI, $[M]^+$, $C_{10}H_7N_2F$) calcd.: 174.0588, found: 174.0589.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-MKFPRHAKYB-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/MKFPRHAKYBHQEB-UHFFFAOYSA-N.1

2-Trifluoromethyl-4,4′-bipyridine (3 b): 4-Iodopyridine (471 mg, 2.30 mmol, 1.00 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine (691 mg, 2.53 mmol, 1.10 equiv), dipotassium carbonate (795 mg, 5.75 mmol, 2.50 equiv), triphenylphosphine (60.3 mg, 230 µmol, 0.100 equiv) and palladium(II) acetate (25.8 mg, 115 µmol, 0.0500 equiv) were combined with a degassed mixture of tetrahydrofuran (10.0 mL) and water (2.00 mL). After stirring for 19 h at 70 °C, the mixture was cooled to 21 °C, and following the general procedure, the title compound (434 mg, 1.93 mmol, 84% yield) as a colorless solid was obtained. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.84 (d, J = 5.1 Hz, 1H, 6-C*H*), 8.80–8.75 (m, 2H, 2′- and 6′-C*H*), 7.90 (d, J = 1.7 Hz, 1H, 3-C*H*), 7.72 (dd, J = 5.1, 1.7 Hz, 1H, 5-C*H*), 7.57–7.53 (d, J = 4.6 Hz, 2H, 3′- and 5′-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 151.1 (d, J = 5.9 Hz, 2 C, 2′- and 6′-*C*H), 149.5 (q, J = 34.9 Hz, 2-C_q-CF_3), 147.6 (), 144.3 (4′-C_q), 132.7 (d, J = 104.0 Hz), 124.2 (5-*C*H), 121.5 (2 C, 3′- and 5′-*C*H), 121.5 (q, J = 274.5 Hz, 2-*C*CF_3), 118.5 (q, J = 2.8 Hz, 3-*C*H) ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = -68.0 (2-CF_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3210 (w), 3197 (w), 3163 (w), 3098 (w), 3085 (w), 3061 (w), 3044 (w), 2951 (w), 2922 (w), 2866 (w), 1741 (vw), 1595 (m), 1540 (w), 1426 (m), 1409 (m), 1341 (m), 1327 (s), 1305 (w), 1269 (m), 1237 (w), 1224 (m), 1186 (vs), 1120 (vs), 1109 (vs), 1086 (vs), 1054 (vs), 1028 (m), 987 (m), 969 (w), 905 (m), 873 (m), 850 (w), 836 (m), 819 (vs), 755 (w), 745 (m), 721 (m), 696 (m), 686 (vs), 654 (m), 613 (vs), 584 (m), 552 (m), 540 (s), 518 (vs), 462 (w), 433 (w), 418 (m), 402 (w). MS (EI, 70 eV) m/z (%) = 225 (11) $[M+H]^+$, 224 (100) $[M]^+$, 223 (3) $[M-H]^+$, 205 (3), 203 (4), 156 (3), 155 (25), 128 (4), 102 (4), 101 (3), 51 (3). HRMS (EI, $[M]^+$, $C_{11}H_7N_2F_3$) calcd.: 224.0556, found: 224.0555.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-YIYSY-LUFLW-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/YIYSYLUFLWDJHV-UHFFFAOYSA-N.1

2-Methyl-4,4′-bipyridine (3 c): 4-Bromo-2-methylpyridine (500 mg, 2.91 mmol, 1.00 equiv), pyridin-4-ylboronic acid (429 mg, 3.49 mmol, 1.20 equiv), potassium phosphate (1.23 g, 5.81 mmol, 2.00 equiv), tricyclohexylphosphane (81.5 mg, 291 µmol, 0.100 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (150 mg, 145 µmol, 0.0500 equiv) were combined with a degassed mixture of 1,4-dioxane (14.0 mL) and water (6.00 mL). After stirring for 17.5 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 5% MeOH to afford the title compound (681 mg, 4.00 mmol, 99% yield) and was obtained as a yellow solid. ^{1}H NMR (500 MHz, CD_2Cl_2, ppm) δ = 8.72–8.67 (m, 2H, 2′- and 6′-C*H*), 8.58 (dd, J = 5.2, 0.8 Hz, 1H, 6-C*H*), 7.58–7.49 (m, 2H, 3′- and 5′-C*H*), 7.41 (s, 1H, 3-C*H*), 7.35 (dd, J = 5.2, 2.0 Hz, 1H, 5-C*H*), 2.61 (s, 3H, CH_3). ^{13}C NMR (126 MHz, CD_2Cl_2, ppm) δ = 160.0 (2-C*q*), 151.0 (2′- and 6′-*C*H, 2 C), 150.3 (6-*C*H), 146.1 (4′-C*q*), 146.0 (4-C*q*), 121.8 (3′- and 5′-*C*H, 2 C), 121.2 (3-*C*H), 118.8 (5-*C*H), 24.7 (CH_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3026 (m), 2979 (w), 2972 (w), 2963 (w), 2919 (m), 2884 (w), 2850 (w), 1592 (vs), 1536 (m), 1473 (m), 1459 (w), 1445 (m), 1419 (w), 1412 (w), 1392 (s), 1370 (w), 1290 (w), 1217 (w), 1211 (w), 986 (s), 858 (m), 815 (vs), 618 (vs), 601 (m), 552 (m), 528 (vs), 448 (s), 401 (vs). MS (EI, 70 eV) m/z (%) = 171 (10) $[M+H]^+$, 170 (100) $[M]^+$, 169 (9) $[M-H]^+$. HRMS (EI, $[M]^+$, $C_{11}H_{10}N_2$) calcd.: 170.0838, found: 170.0838.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-YQBPLVKHEZ-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/YQBPLVKHEZNFMQ-UHFFFAOYSA-N.1

3-Methyl-4,4′-bipyridine (3 d): 4-Bromo-3-methylpyridine hydrochloride (834 mg, 4.00 mmol, 1.00 equiv), pyridin-4-ylboronic acid (590 mg, 4.80 mmol, 1.20 equiv), potassium phosphate (2.55 g, 12.0 mmol, 3.00 equiv), tricyclohexylphosphane (112 mg, 401 µmol,

0.100 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (207 mg, 200 μmol, 0.0499 equiv) were combined with a degassed mixture of 1,4-dioxane (14.0 mL) and water (6.00 mL). After stirring for 17.5 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (674 mg, 3.96 mmol, 99% yield) was obtained as an orange solid. ^{1}H NMR (500 MHz, CD_2Cl_2, ppm) δ = 8.70–8.64 (m, 2H, 2′- and 6′-C*H*), 8.52 (s, 1H, 2-C*H*), 8.48 (d, J = 4.9 Hz, 1H, 6-C*H*), 7.29–7.24 (m, 2H, 3′- and 5′-C*H*), 7.14 (d, J = 4.9 Hz, 1H, 5-C*H*), 2.27 (s, 3H, CH_3). ^{13}C NMR (126 MHz, CD_2Cl_2, ppm) δ = 152.0 (2-*C*H), 150.4 (2′- and 6′-*C*H, 2 C), 148.0 (6-*C*H), 147.2 (4′-C_q), 146.7 (4-C_q), 130.6 (3-C_q), 123.8 (3′- and 5′-*C*H, 2 C), 123.6 (5-*C*H), 17.2 (CH_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 2922 (m), 2849 (w), 1585 (s), 1557 (w), 1537 (w), 1480 (m), 1446 (m), 1407 (vs), 1378 (m), 1303 (w), 1215 (w), 1159 (m), 1079 (w), 1057 (w), 1040 (w), 989 (m), 856 (w), 829 (vs), 813 (s), 759 (w), 751 (w), 734 (w), 626 (s), 581 (vs), 534 (vs), 494 (w), 479 (w), 475 (w), 443 (w), 433 (m), 409 (w), 394 (m). MS (EI, 70 eV) m/z (%) = 171 (13) $[M+H]^+$, 170 (100) $[M]^+$, 169 (53) $[M-H]^+$, 168 (7), 143 (31), 142 (17), 141 (5), 117 (5), 115 (12), 89 (5). HRMS (EI, $[M]^+$, $C_{11}H_{10}N_2$) calcd.: 170.0838, found: 170.0840.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-NFNMQYQMQP-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/NFNMQYQMQPNCKT-UHFFFAOYSA-N.1

[4,4′-Bipyridin]-2-ylmethanol (3e): (4-Bromopyridin-2-yl)methanol (230 mg, 1.22 mmol, 1.00 equiv), 4-pyridylboronic acid (226 mg, 1.83 mmol, 1.50 equiv), 4 M aqueous solution of sodium carbonate (972 mg, 9.17 mmol, 7.50 equiv) and palladium triphenylphosphane (141 mg, 122 μmol, 0.100 equiv) were combined with degassed 1,2-dimethoxyethane (5.00 mL). After stirring for 20 h at 100 °C, the reaction mixture was cooled to 21 °C, extracted with ethyl acetate, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 5% MeOH to yield the title compound (158 mg, 851 μmol, 70% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.78–8.71 (m, 2H, 2′- and 6′-C*H*), 8.68 (dd, J = 5.2, 0.9 Hz, 1H, 6-C*H*), 7.56–7.53 (m, 2H, 3′- and 5′-C*H*), 7.53–7.51 (m, 1H, 3-C*H*), 7.47–7.43 (m, 1H, 5-C*H*), 4.87 (s, 2H, CH_2), 3.62 (s, 1H, O*H*). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 160.5 (2-C_q), 150.9 (2 C, 2′- and 6′-*C*H), 149.6 (6-*C*H), 146.6 (4-C_q), 145.7 (4′-C_q), 121.6 (2 C, 3′- and 5′-*C*H), 120.4 (5-*C*H), 118.3 (3-*C*H), 64.5 (CH_2). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3123 (m), 3047 (m), 3030 (m), 2969 (w), 2945 (w), 2919 (w), 2866 (w), 2829 (m), 2825 (m), 2715 (w), 2645 (w), 2639 (w), 1608 (w), 1592 (vs), 1567 (m), 1536 (s), 1499 (w), 1479 (w), 1442 (w), 1421 (w), 1401 (vs), 1364 (s), 1332 (w), 1303 (m), 1241 (w), 1215 (w), 1207 (w), 1118 (w), 1078 (w), 1065 (w), 1033 (vs), 1006 (m), 989 (m), 973 (m), 912 (m), 877 (w), 863 (m), 822 (vs), 745 (s), 732 (s), 674 (w), 660 (w), 618 (vs), 575 (vs), 540 (vs), 518 (m), 463 (vs), 428 (w), 405 (m), 382 (w). MS (EI, 70 eV) m/z (%) = 281 (12), 269 (17), 231 (15), 219 (22), 187 (11) $[M+H]^+$, 186 (86) $[M]^+$, 185 (100) $[M-H]^+$, 181 (27), 169 (31), 157 (41), 156 (21), 155 (26), 131 (27), 119 (27), 100 (6), 77 (6), 69 (85), 51 (6). HRMS (EI, $[M]^+$, $C_{11}H_{10}N_2O$) calcd.: 186.0788, found: 186.0786.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-IPEARMYLWJ-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/IPEARMYLWJENPB-UHFFFAOYSA-N.2

4-(Pyridin-4-yl)quinoline (3f): 4-Bromoquinoline (500 mg, 2.88 mmol, 1.00 equiv), pyridin-4-ylboronic acid (355 mg, 2.88 mmol, 1.20 equiv), tris(dibenzylidenaceton)dipalladium chloroform (149 mg, 144 μmol, 0.0500 equiv), tricyclohexylphosphane (80.9 mg, 288 μmol, 0.100 equiv) and potassium carbonate (1.02 g, 4.81 mmol, 2.00 equiv) were combined with a degassed mixture of dioxane (7.0 mL) and water (3.00 mL). After stirring 18 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (448 mg, 2.17 mmol, 90% yield) as a yellow hygroscopic solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.98 (d, ^3J = 4.4 Hz, 1H, C*H*), 8.82–8.75 (m, 2H, C*H*), 8.20 (d, ^3J = 8.4 Hz, 1H, C*H*), 7.81 (dd, ^3J = 8.4, 1.8 Hz, 1H, C*H*), 7.76 (ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.4 Hz, 1H, C*H*), 7.54 (ddd, ^3J = 8.4, 6.9 Hz, ^4J = 1.4 Hz, 1H, C*H*), 7.46–7.41 (m, 2H, C*H*), 7.32 (d, ^3J = 4.3 Hz, 1H, C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 150.3 (2^{Py},6^{Py}-*C*H, 2 C), 150.1 (2^{Ch}-*C*H, 1 C), 148.8 ($8a^{Ch}$-C_q, 1 C), 146.0 (4^{Py}-C_q, 1 C), 145.6 (4^{Ch}-C_q, 1 C), 130.3 (8^{Ch}-*C*H, 1 C), 129.9 (7^{Ch}-CH_{Ar}, 1 C), 127.4 (6^{Ch}-*C*H, 1 C), 125.9 ($4a^{Ch}$-C_q, 1 C), 125.1 (5^{Ch}-*C*H, 1 C), 124.4 (3^{Py},5^{Py}-*C*H, 2 C), 121.1 (3^{Ch}-*C*H, 1 C). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3068 (w), 3031 (w), 2999 (w), 2925 (w), 2850 (w), 1935 (vw), 1581 (s), 1407 (m), 833 (s), 815 (s), 776 (vs), 609 (vs), 568 (vs), 414 (s). MS (EI, 70 eV) m/z (%) = 207 (13) $[M+H]^+$, 206 (100) $[M]^+$, 205 (65) $[M-H]^+$, 179 (7), 178 (11), 152 (5), 151 (11), 58 (6). HRMS (EI, $[M]^+$, $C_{14}H_{10}N_2$) calcd.: 206.0838, found: 206.0839.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-CZZRMJRYEA-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/CZZRMJRYEAIGTJ-UHFFFAOYSA-N.2

2,6-Difluoro-4,4′-bipyridine (3g): 2,6-Difluoro-4-iodopyridine (1.10 g, 4.56 mmol, 1.00 equiv), pyridin-4-ylboronic acid (673 mg, 5.48 mmol, 1.20 equiv), potassium carbonate (1.94 g, 9.13 mmol, 2.00 equiv), tricyclohexylphosphane (128 mg, 456 μmol, 0.100 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (236 mg, 228 μmol, 0.0500 equiv) were combined with a degassed mixture of tetrahydrofuran (20.0 mL) and water (4.00 mL). After stirring 18 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (736 mg, 3.83 mmol, 84% yield) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.69–8.66 (m, 2H, 2′- and 6′-C*H*), 7.52–7.47 (m, 2H, 3- and 5-C*H*), 7.04 (s, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 162.4 (dd, J = 248 Hz, J = 15.8 Hz, 2 C, 2- and 6-*C*F), 155.4 (dd, J = 8.0 Hz, 4′-C_q), 150.5 (2 C, 2′-*C*H and 6′-CH), 144.0 (dd, J = 3.2 Hz, 4-C_q), 121.6 (2 C, 3′-*C*H and 5′-CH), 104.5–104.1 (m, 2 C, 3- and 5- *C*H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = -66.8 (2- and 6-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3072, 3027, 2959, 2922, 2898, 2851, 1945, 1625, 1598, 1575, 1551, 1531, 1506, 1439, 1425, 1404, 1361, 1336, 1266, 1220, 1210, 1128, 1078, 1027, 992, 967, 877, 822, 650, 642, 608, 551, 479.

MS (EI, 70 eV) m/z (%) = 193 (12%) $[M+H]^+$, 192 (100%) $[M]^+$, 191 (23%) $[M-H]^+$, 190 (31%), 181 (17%), 162 (16%). HRMS (EI, $[M]^+$, $C_{10}H_6F_2N_2$) calcd.: 192.0499, found: 192.0500.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-HTVXYMSPZM-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/HTVXYMSPZMCSRI-UHFFFAOYSA-N.1

2,6-Dimethyl-4,4′-bipyridine (3h): 4-Bromo-2,6-dimethylpyridine (501 mg, 2.69 mmol, 1.00 equiv), pyridin-4-ylboronic acid (397 mg, 3.23 mmol, 1.20 equiv), potassium carbonate (1.14 g, 5.39 mmol, 2.00 equiv), tricyclohexylphosphane (75.5 mg, 269 μmol, 0.0999 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (139 mg, 134 μmol, 0.0499 equiv) were combined with a degassed mixture of 1,4-dioxane (7.0 mL) and water (3.00 mL). After stirring for 17.5 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (496 mg, 2.69 mmol, 100% yield) as an orange hygroscopic solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta = 8.73–8.67$ (m, 2H, 2′- and 6′-C*H*), 7.53–7.47 (m, 2H, 3′- and 5′-C*H*), 7.19 (s, 2H, 3- and 5-C*H*), 2.61 (s, 6H, 2- and 6-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 158.9$ (2- and 6-C_q), 150.7 (2′- and 6′-CH), 146.3-146.3 (4- and 4′-C_q), 121.6 (3′- and 5′-CH), 118.2 (3- and 5-CH), 24.8 (2- and 6-CH_3). IR (ATR, cm^{-1}) $\tilde{\nu} = 3027$ (w), 2980 (w), 2921 (m), 2851 (w), 1595 (vs), 1572 (s), 1541 (vs), 1395 (s), 1215 (m), 989 (m), 819 (vs), 647 (vs), 561 (s), 459 (s). MS (EI, 70 eV) m/z (%) = 185 (15) $[M+H]^+$, 184 (100) $[M]^+$, 183 (6) $[M-H]^+$, 168 (4), 142 (4), 115 (6). HRMS (EI, $[M]^+$, $C_{12}H_{12}N_2$) calcd.: 184.0995, found: 184.0995.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-NBOYKYKOJI-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/NBOYKYKOJICEIQ-UHFFFAOYSA-N.1

2,6-Dichloro-4,4′-bipyridine (3i): 2,6-Dichloro-4-iodopyridine (500 mg, 1.83 mmol, 1.00 equiv), pyridin-4-ylboronic acid (270 mg, 2.20 mmol, 1.20 equiv), tricyclohexylphosphane (61.4 mg, 219 μmol, 0.120 equiv), potassium phosphate (775 mg, 3.65 mmol, 2.00 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (18.9 mg, 18.3 μmol, 0.0100 equiv) were combined with a degassed mixture of dioxane (8.0 mL) and water (3.00 mL). After stirring 18 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via automatic flash-chromatography on silica gel using DCM with 1% to 11% MeOH to yield the title compound (305 mg, 1.36 mmol, 74%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta = 8.81–8.75$ (m, 2H, 2′- and 6′-C*H*), 7.50 (s, 2H, 3- and 5-C*H*), 7.49–7.47 (m, 2H, 3′- and 5′-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 151.7$ (2- and 6-C_q), 151.2 (4-C_q), 151.2 (2′- and 6′-CH), 143.2 (4′-C_q), 121.4 (3- and 5-CH), 121.0 (3′- and 5′-CH). IR (ATR, cm^{-1}) $\tilde{\nu} = 3041$ (w), 2928 (w), 1943 (vw), 1578 (vs), 1519 (s), 1366 (vs), 1171 (s), 1125 (s), 982 (w), 881 (w), 809 (vs), 628 (vs), 547 (m), 462 (w), 432 (m). MS (EI, 70 eV, 20 °C, %) *m/z* = 228 (11) [M ($^{37}Cl_2$)]$^+$, 227 (7), 226 (62) [M ($^{37}Cl^{35}Cl$)]$^+$, 225 (12), 224 (100) [M ($^{35}Cl_2$)]$^+$, 191 (15) $[M-Cl]^+$, 190 (6), 189 (44) $[M-Cl]^+$, 127 (16), 126 (9), 51 (13). HRMS (EI, $[M]^+$, $C_{10}H_6N_2{}^{35}Cl_2$) calcd.: 223.9903, found: 223.9904.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-FLZJZVAEYW-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/FLZJZVAEYWUCET-UHFFFAOYSA-N.1

3,5-Dichloro-4,4′-bipyridine (3j): 3,5-Dichloro-4-iodopyridine (500 mg, 1.83 mmol, 1.00 equiv), pyridin-4-ylboronic acid (270 mg, 2.19 mmol, 1.20 equiv), tris(dibenzylidenaceton)dipalladium chloroform (94.8 mg, 91.6 μmol, 0.0502 equiv), tricyclohexylphosphane (61.7 mg, 220 μmol, 0.121 equiv) and potassium carbonate (776 mg, 3.65 mmol, 2.00 equiv) were combined with a degassed mixture of dioxane (8.0 mL) and water (3.00 mL). After stirring 18 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (284 mg, 1.26 mmol, 69% yield) as yellow crystals. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta = 8.80–8.77$ (m, 2H, 2′- and 6′-C*H*), 8.62 (s, 2H, 2- and 6-C*H*), 7.24–7.21 (m, 2H, 3′- and 5′-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 150.3$ (2 C, 2′- and 6′-C_q), 148.0 (2 C, 2- and 6-C_q), 144.0 (4-C_q), 141.8 (4′-C_q), 131.2 (2 C, 3- and 5- C_q), 123.6 (2 C, 3′ and 5′-CH). IR (ATR, cm^{-1}) $\tilde{\nu} = 3070$ (vw), 3026 (vw), 2925 (w), 2850 (w), 1963 (vw), 1868 (vw), 1817 (w), 1718 (vw), 1601 (w), 1544 (m), 1412 (m), 1401 (m), 1384 (s), 1218 (s), 1205 (s), 884 (m), 800 (vs), 748 (s), 632 (s), 581 (vs). MS (EI, 70 eV) m/z (%) = 228 (10) [M ($^{37}Cl_2$)]$^+$, 227 (6), 226 (59) [M ($^{37}Cl^{35}Cl$)]$^+$, 225 (12), 224 (100) [M ($^{35}Cl_2$)]$^+$, 191 (6) $[M-Cl]^+$, 189 (20) $[M-Cl]^+$, 162 (8), 153 (12), 127 (9), 126 (9), 99 (11), 74 (11), 51 (7). HRMS (EI, $[M]^+$, $C_{10}H_6N_2{}^{35}Cl_2$) calcd.: 223.9903, found: 223.9902.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-IYZHCNYWKB-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ.1

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/IYZHCNYWKBJXSF-UHFFFAOYSA-N.2

2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine: 4-Bromo-2,6-dimethyl-pyridine (1.00 g, 5.37 mmol, 1.00 equiv), B_2Pin_2 (1.50 g, 5.91 mmol, 1.10 equiv), palladium(II) acetate (60.3 mg, 269 μmol, 0.0500 equiv), tricyclohexylphosphane (151 mg, 537 μmol, 0.100 equiv) and potassium acetate (1.32 g, 13.4 mmol, 2.50 equiv) were combined with degassed dioxane (20 ml). After stirring for 18 h at 110 °C, the mixture was cooled to 21 °C and filtered through a short plug of Celite® with DCM. The solvent was removed under reduced pressure, and the crude was redissolved in chloroform. It was washed with water, dried over sodium sulfate, and suspended over activated charcoal (2.0 g) for two hours. It was filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via sublimation at 0.100 mbar and 65 °C to yield 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (804 mg, 3.45 mmol, 64% yield) as white hygroscopic crystals. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta = 7.30$ (s, 2H, 3- and 5-C*H*), 2.52 (s, 6H, 2- and 6-CH_3), 1.34 (s, 12H, 4×CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 157.2$ (2 C, 2- and 6-C_q), 125.4 (2 C, 3- and 5-CH), 84.5 (2 C, 2×$C_q(CH_3)_2$), 25.0 (4 C, 4×

CH_3), 24.3 (2 C, 2- and 6-CH_3). 4-C_q not visible due to boron. IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3048 (vw), 2978 (m), 2928 (w), 1632 (w), 1548 (w), 1519 (w), 1473 (w), 1452 (w), 1390 (vs), 1371 (vs), 1358 (vs), 1322 (vs), 1249 (s), 1213 (m), 1163 (m), 1142 (vs), 1116 (vs), 1007 (w), 983 (w), 963 (m), 891 (m), 871 (w), 849 (vs), 734 (m), 694 (w), 674 (vs), 578 (w), 562 (w), 523 (w), 449 (w), 414 (w). MS (EI, 70 eV) m/z (%) = 234 (10), 233 (70) $[M(^{11}B)+H]^+$, 232 (18) $[M(^{11}B)]^+$, 231 (8) $[M(^{10}B)]^+$, 218 (33), 217 (8), 181 (41), 176 (8), 148 (13), 147 (100), 134 (33), 133 (37), 132 (11), 131 (43), 129 (13), 119 (8), 100 (9), 69 (78), 59 (14), 58 (13). HRMS (EI, $[M]^+$, $C_{13}H_{20}O_2N^{11}B$) calcd.: 233.1582, found: 233.1581.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-XYNDKPYVNT-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/XYNDKPYVNTVDAH-UHFFFAOYSA-N.1

2′,6′-Dimethyl-[4,4′-bipyridin]-3-amine (3 k): 4-Bromopyridin-3-amine (215 mg, 1.24 mmol, 1.00 equiv), 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (348 mg, 1.49 mmol, 1.20 equiv), potassium phosphate (527 mg, 2.48 mmol, 2.00 equiv), tricyclohexylphosphane (34.8 mg, 124 µmol, 0.0999 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (64.2 mg, 62.0 µmol, 0.0499 equiv) were combined with a degassed mixture of 1,4-dioxane (5.00 mL) and Water (2.10 mL). After stirring for 17.5 h at 90 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (115 mg, 577 µmol, 46% yield) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.18 (s, 1H, 2-C*H*), 8.08 (d, J = 4.9 Hz, 1H, 6-C*H*), 7.06 (s, 2H, 3′- and 5′-C*H*), 7.00 (d, J = 4.9 Hz, 1H, 5-C*H*), 3.80 (s, 2H, NH_2), 2.59 (s, 6H, 2′- and 6′-CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 159.0 (2 C, 2′- and 6′-C_q), 145.6 (C_q), 140.4 (6-CH), 139.5 (C_q), 138.6 (2-CH), 131.2, 123.6 (5-CH), 119.7 (2 C, 3′- and 5′-CH), 24.8 (2 C, 2′- and 6′-CH_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3336 (m), 3160 (s), 2921 (w), 2850 (w), 1738 (vw), 1656 (w), 1608 (s), 1588 (s), 1565 (vs), 1541 (s), 1500 (m), 1422 (vs), 1400 (vs), 1374 (m), 1324 (s), 1295 (m), 1238 (s), 1220 (s), 1064 (s), 1028 (m), 870 (m), 815 (vs), 759 (m), 735 (m), 664 (m), 653 (vs), 626 (s), 596 (m), 572 (s), 551 (s), 540 (vs), 518 (s), 480 (s), 463 (m), 449 (s), 409 (m), 394 (m). MS (EI, 70 eV) m/z (%) = 200 (14) $[M+H]^+$, 199 (100) $[M]^+$, 198 (15) $[M-H]^+$, 184 (10), 169 (5), 158 (6), 157 (8), 69 (13). HRMS (EI, $[M]^+$, $C_{12}H_{13}N_3$) calcd.: 199.1104, found: 199.1104.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-KKCLKIWLYC-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/KKCLKIWLYCRTCT-UHFFFAOYSA-N.1

(E)-2,6-Dimethyl-3′-(phenyldiazenyl)-4,4′-bipyridine (3 l): 2′,6′-Dimethyl-[4,4′-bipyridin]-3-amine (73.0 mg, 366 µmol, 1.00 equiv) was combined with pyridine (1.00 mL), and tetramethylammonium hydroxide (1.07 g, 1.07 mL, 2.93 mmol, 8.00 equiv) solution was added. It was heated up to 80 °C, and a solution of nitrosobenzene (58.9 mg, 57.7 µL, 550 µmol, 1.50 equiv) in pyridine (1.5 mL) was slowly added over 60 minutes *via* a syringe pump. After stirring for another 4 hours at 80 °C, it was extracted with ethyl acetate and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 6% MeOH in darkness to yield the title compound (98.4 mg, 341 µmol, 93% yield) as a purple solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.90 (s, 1H, 2′-C*H*), 8.75 (d, ^3J = 5.1 Hz, 1H, 6′-C*H*), 7.85–7.78 (m, 2H, 2×phenyl-C*H*), 7.53–7.49 (m, 3H, 3×phenyl-C*H*), 7.48 (d, ^3J = 5.1 Hz, 1H, 5′-C*H*), 7.09 (s, 2H, 3- and 5-C*H*), 2.60 (s, 6H, 2×CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 157.8 (2 C, 2- and 6-C_q), 152.8 (phenyl-C_q), 151.4 (6′-CH), 144.8, 144.7 (2 C), 138.8 (2′-CH), 132.1 (phenyl-CH), 129.4 (2 C, 2×phenyl-CH), 124.1 (5′-CH), 123.5 (2 C, 2×phenyl-CH), 121.7 (2 C, 3- and 5-CH), 24.7 (2 C, 2- and 6-CH_3). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3036 (w), 3004 (w), 2918 (w), 1606 (w), 1582 (s), 1568 (m), 1536 (s), 1489 (w), 1468 (w), 1458 (w), 1445 (w), 1409 (w), 1390 (m), 1303 (w), 1227 (w), 1207 (w), 1186 (w), 1149 (w), 1055 (w), 1030 (w), 1021 (w), 999 (w), 980 (w), 933 (w), 873 (w), 837 (vs), 810 (w), 778 (m), 755 (vs), 731 (w), 690 (vs), 647 (s), 622 (w), 613 (w), 584 (m), 567 (m), 537 (vs), 514 (vs), 470 (m), 435 (w), 409 (w). MS (EI, 70 eV) m/z (%) = 316 (8), 315 (10), 289 (21) $[M+H]^+$, 288 (100) $[M]^+$, 273 (24), 184 (7), 183 (35), 168 (13), 167 (10), 121 (14), 115 (7), 105 (39), 77 (87), 69 (12), 58 (9).HRMS (EI, $[M]^+$, $C_{18}H_{16}N_4$) calcd.: 206.0838, found: 206.0839.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-WKKIRCHZQJ-UHFFFADPSC-NUHFF-NBDJD-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/WKKIRCHZQJWBFT-QURGRASLSA-N.1

4-(4-Bromo-2-nitrophenyl)pyridine: 4-Bromo-1-iodo-2-nitrobenzene (328 mg, 1.00 mmol, 1.00 equiv), 4-pyridylboronic acid (123 mg, 1.00 mmol, 1.00 equiv), potassium carbonate (276 mg, 2.00 mmol, 2.00 equiv), triphenylphosphine (26.2 mg, 100 µmol, 0.100 equiv) and palladium(II) acetate (33.7 mg, 150 µmol, 0.150 equiv) were combined with a degassed mixture of THF (20.0 mL) and water (10 ml). After stirring for 18 h at 80 °C, the reaction mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using cyclohexane and ethyl acetate (20:1→0:1) to yield the title compound (184 mg, 659 µmol, 66% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.74 – 8.63 (m, 2H, 2- and 6-C*H*), 8.13 (d, J = 2.0 Hz, 1H, 3-ph-C*H*), 7.82 (dd, J = 8.2, 2.0 Hz, 1H, 5-ph-C*H*), 7.30 (d, J = 8.2 Hz, 1H, 6-ph-C*H*), 7.23 – 7.19 (m, 2H, 3- and 5-C*H*). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ = 150.3 (2 C, 3- and 5-CH), 149.0 (2-ph-C_q-NO_2), 144.8 (4-C_q), 136.1 (5-ph-CH), 133.0 (1-ph-C_q), 132.9 (6-ph-CH), 127.8 (3-ph-CH), 123.1 (4-ph-CBr), 122.7 (2 C, 3- and 5-CH). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3031 (w), 2995 (w), 2966 (w), 2931 (w), 2854 (w), 1599 (m), 1520 (vs), 1472 (s), 1408 (s), 1353 (vs), 1327 (m), 1295 (m), 1268 (m), 1217 (s), 1152 (m), 1095 (m), 1069 (m), 1021 (w), 994 (m), 967 (w), 928 (s), 871 (s), 841 (m), 823 (m), 810 (vs), 768 (vs), 761 (vs), 720 (m), 674 (m), 666 (m), 642 (m), 603 (s), 555 (s), 526 (vs), 458 (w), 436 (vs), 415 (s), 388 (m). MS (EI, 70 eV) m/z (%) = 281 (15) [M (^{81}Br)+H]$^+$, 280 (77) [M (^{81}Br)]$^+$, 278 (78) [M (^{79}Br)]$^+$, 253 (14), 252 (100), 251 (22), 250 (94), 225 (24), 224 (15), 223 (31), 222 (14), 197 (15), 195 (21), 169 (14), 153 (17), 126 (42), 116 (21). HRMS (EI, $[M]^+$, $C_{11}H_7{}^{79}BrN_2O_2$) calcd.: 277.9685, found: 277.9684.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-RCBGSXPNCG-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/RCBGSXPNCGOTBB-UHFFFAOYSA-N.1

2,6-Difluoro-4-(3-nitro-4-(pyridin-4-yl)phenyl)pyridine (3 m): 4-(4-Bromo-2-nitrophenyl)pyridine (278 mg, 996 μmol, 1.00 equiv), (2,6-difluoropyridin-4-yl)boronic acid (174 mg, 1.10 mmol, 1.10 equiv), potassium phosphate (423 mg, 1.99 mmol, 2.00 equiv) tricyclohexylphosphane (33.5 mg, 120 μmol, 0.120 equiv) and tris(dibenzylidenaceton)dipalladium chloroform (51.6 mg, 49.8 μmol, 0.0500 equiv) were combined with a degassed mixture of dioxane (3.0 mL) and water (7.0 mL). After stirring 18 h at 100 °C, the mixture was cooled to 21 °C, extracted with DCM, and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 5% MeOH to yield the title compound (496 mg, 2.69 mmol, 100% yield) as an orange hygroscopic solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta =$ 8.73 (d, $J = 5.2$ Hz, 2H, 2′- and 6′-C*H*), 8.23 (d, $J = 1.9$ Hz, 1H, 2-ph-C*H*), 7.93 (dd, $J = 8.0$, 1.9 Hz, 1H, 6-ph-C*H*), 7.60 (d, $J = 7.9$ Hz, 1H, 5-ph-C*H*), 7.29–7.27 (m, 2H, 3′- and 5′-C*H*), 7.11 (s, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 162.7$ (dd, $J = 247.7$, 16.1 Hz, 2 C, 2- and 6-C*F*), 154.9 (dd, $J = 8.2$ Hz, 4-C_q), 150.4 (2 C, 2′- and 6′-*C*H), 149.3 (3-ph-C_q-NO_2), 144.7 (4-C_q), 137.9 (dd, $J = 3.4$ Hz, 1-ph-C_q), 135.6 (4-ph-C_q), 132.9 (5-ph-*C*H), 131.2 (6-ph-*C*H), 123.4 (2-ph-*C*H), 122.7 (2 C, 3′- and 5′-C*H*), 105.4–103.5 (m, 2 C, 3- and 5-C*H*). ^{19}F NMR (471 MHz, $CDCl_3$, ppm) $\delta =$-66.3 (2- and 6-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu} =$ 3036 (w), 1618 (vs), 1596 (s), 1572 (w), 1555 (m), 1536 (vs), 1492 (w), 1462 (w), 1422 (vs), 1398 (w), 1375 (m), 1361 (vs), 1262 (w), 1218 (m), 1200 (w), 1163 (w), 1072 (w), 1030 (m), 997 (w), 936 (w), 895 (w), 877 (w), 864 (w), 851 (m), 833 (m), 823 (vs), 765 (m), 752 (s), 722 (w), 683 (w), 666 (w), 635 (w), 594 (w), 561 (w), 538 (w), 514 (m), 435 (w), 419 (w). MS (EI, 70 eV) m/z (%) = 319 (30), 313 (39) $[M]^+$, 285 (44), 281 (18), 269 (36), 239 (19), 231 (23), 230 (27), 219 (46), 181 (27), 169 (55), 131 (29), 119 (33), 69 (100). HRMS (EI, $[M]^+$, $C_{16}H_9O_2N_3F_2$) calcd.: 313.0657, found: 313.0655.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-HHU-KIRVIJW-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/HHUKIRVIJWOCCO-UHFFFAOYSA-N.1

5-(2,6-Difluoropyridin-4-yl)-2-(pyridin-4-yl)aniline (3 n): 2,6-Difluoro-4-(3-nitro-4-(pyridin-4-yl)phenyl)pyridine (507 mg, 1.62 mmol, 1.00 equiv) was dissolved in a solution of DCM (20.0 mL), and MeOH (10.0 mL) and 10% palladium on charcoal (170 mg, 160 μmol, 9.9 mol%) was added. The reaction was stirred for 5 hours at 21 °C in the high-pressure reactor under an H_2 atmosphere at 50 bar. The crude product was filtered through a plug of Celite® with DCM and MeOH. The solvent was removed under reduced pressure, and the obtained crude product was purified *via* flash-chromatography on silica gel using DCM with 2% to 15% MeOH to yield the title compound (451 mg, 1.59 mmol, 98% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta =$ 8.75–8.69 (m, 2H, 2′- and 6′-C*H*), 7.46–7.42 (m, 2H, 3′- and 5′-C*H*), 7.25 (d, $J = 7.8$ Hz, 5-ph-C*H*), 7.07 (dd, $J = 7.9$, 1.8 Hz, 6-ph-C*H*), 7.02 (s, 2H, 3- and 5-C*H*), 7.00 (d, $J = 1.8$ Hz, 2-ph-C*H*), 4.01 (br s, 2H, NH_2). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 162.4$ (dd, $J = 245.8$, 16.4 Hz, 2 C, 2- and 6-C*F*), 159.1 (dd, $J = 8.1$, 4-C_q) 150.7 (2 C, 2′- and 6′-*C*H), 146.6 (4-ph-C_q), 144.3 (3-ph-C_q-NH_2), 137.8 (dd, $J = 3.2$ Hz, 1-ph-C_q), 131.2 (5-ph-*C*H), 126.2 (4′-C_q), 123.8 (2 C, 3′- and 5′-*C*H), 117.5 (6-ph-*C*H), 114.3 (2-ph-*C*H), 104.5–103.4 (m, 2 C, 3- and 5-C*H*). ^{19}F NMR (471 MHz, $CDCl_3$, ppm) $\delta =$-68.5 (2- and 6-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu} =$ 3353 (w), 3336 (w), 3330 (w), 3320 (w), 3216 (w), 1616 (vs), 1596 (vs), 1550 (vs), 1520 (m), 1462 (m), 1434 (m), 1398 (vs), 1361 (m), 1327 (m), 1310 (m), 1296 (s), 1266 (m), 1204 (s), 1187 (s), 1164 (m), 1119 (w), 1108 (w), 1091 (w), 1068 (w), 1026 (vs), 994 (s), 966 (m), 881 (w), 871 (m), 849 (vs), 833 (m), 802 (vs), 758 (s), 747 (s), 728 (vs), 718 (s), 698 (s), 671 (s), 652 (s), 643 (s), 616 (s), 588 (vs), 568 (vs), 541 (s), 533 (vs), 496 (s), 483 (s), 462 (vs), 432 (s), 416 (s), 409 (s), 399 (s), 388 (s), 382 (s), 375 (s). MS (EI, 70 eV) m/z (%) = 381 (6), 369 (6), 331 (6), 319 (11), 284 (19), 283 (100), 282 (20), 281 (9), 269 (14), 256 (11), 231 (11), 219 (20), 181 (16), 169 (28), 131 (16), 119 (20), 69 (62). HRMS (EI, $[M]^+$, $C_{16}H_{11}F_2N_3$) calcd.: 283.0916, found: 283.0917.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-ULEBBFUJXV-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/ULEBBFUJXVAYLC-UHFFFAOYSA-N.1

(E)-2,6-Difluoro-4-(3-(phenyldiazenyl)-4-(pyridin-4-yl)phenyl)pyridine (3 o): 5-(2,6-Difluoropyridin-4-yl)-2-(pyridin-4-yl)benzeneamine (120 mg, 424 μmol, 1.00 equiv) was combined with a mixture of pyridine (5.00 mL) and toluene (5.00 mL) before nitrosobenzene (90.7 mg, 89.0 μL, 847 μmol, 2.00 equiv) was added. It was heated up to 60 °C for 4 days before adding more nitrosobenzene (90.7 mg, 89.0 μL, 847 μmol, 2.00 equiv). After stirring for another 18 hours at 80 °C, it was extracted with ethyl acetate and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with 3% to 5% MeOH in darkness to yield the title compound (109 mg, 292 μmol, 69% yield) as a purple solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) $\delta =$ 8.75–8.70 (m, 2H, 2′- and 6′-C*H*), 8.07 (d, 1H, $J = 1.9$ Hz, 2-ph-C*H*), 7.86–7.80 (m, 3H, 2′-ph-C*H*, 6′-ph-C*H* and 6-ph-C*H*), 7.74 (d, 1H, $J = 8.0$ Hz, 5-ph-C*H*), 7.54–7.49 (m, 3H, 3′-ph-C*H*, 5′-ph-C*H* and 4′-ph-C*H*), 7.46–7.43 (m, 2H, 3′- and 5′-C*H*), 7.16 (s, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) $\delta = 162.6$ (2 C, dd, $J = 246.4$, 16.2 Hz, 2- and 6-C*F*), 157.2 (t, $J = 8.0$ Hz, 4-C_q), 152.6 (2′-ph-C_q), 150.0 (3-ph-C_q), 149.5 (2 C, 2′- and 6′-*C*H), 145.8 (4′-C_q), 140.2 (4-ph-C_q), 137.5 (t, $J = 3.3$ Hz, 1-ph-C_q), 132.1 (4′-ph-*C*H), 131.6 (5-ph-*C*H), 129.5 (2 C, 3′-ph-*C*H, and 5′-ph-*C*H), 129.2 (6-ph-C*H*), 125.5 (2 C, 2′- and 6′-C*H*), 123.7 (2 C, 2′-ph-*C*H, and 6′-ph-*C*H), 115.0 (2-ph-*C*H), 104.6–104.0 (m, 2 C, 3- and 5-C*H*). ^{19}F NMR (471 MHz, $CDCl_3$, ppm) $\delta =$-67.7 (2- and 6-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu} =$3043 (w), 2924 (w), 1625 (vs), 1595 (vs), 1572 (m), 1555 (vs), 1536 (w), 1516 (w), 1489 (w), 1459 (m), 1446 (w), 1421 (vs), 1385 (s), 1366 (s), 1309 (w), 1283 (w), 1269 (w), 1254 (w), 1231 (w), 1194 (m), 1163 (w), 1150 (w), 1122 (w), 1071 (w), 1026 (vs), 994 (m), 975 (w), 919 (w), 888 (w), 861 (m), 847 (m), 806 (vs), 765 (m), 748 (vs), 732 (s), 686 (vs), 656 (w), 640 (w), 628 (w), 591 (m), 565 (m), 538 (s), 499 (vs), 467 (w), 455 (w), 443 (w), 429 (w), 416 (m), 398 (w), 384 (w), 375 (w). MS (EI, 70 eV) m/z (%) = 481 (9), 431 (10), 381 (12), 373 (24), 372 (100), 371 (23), 369 (12), 331 (11), 319 (22), 281 (15), 269 (24), 268 (9), 267 (43), 239 (13), 231 (14), 219 (28), 181 (17), 169 (35), 131 (17), 119 (22), 105 (24), 77 (77), 69 (70), 58 (8). HRMS (EI, $[M]^+$, $C_{22}H_{14}F_2N_4$) calcd.: 372.1181, found: 372.1183.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-IHOGTNOTZY-UHFFFADPSC-NUHFF-NYYCM-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/IHOGTNOTZYBLHR-BYYHNAKLSA-N.1

4-Chloropyridine *N*-oxide (5b): 4-Nitropyridine *N*-oxide (**10**) (150 mg, 1.10 mmol, 1.00 equiv) was added portion-wise to acetyl chloride (1.10 g, 1.00 mL, 14.0 mmol, 9.85 equiv). The solution was then heated to 50 °C for 30 minutes, during which a solid precipitated. Ice water was added carefully until all solid material was dissolved. The solution was washed with saturated aqueous sodium carbonate solution and extracted with chloroform. The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The crude product was recrystallized from acetone to give the title compound (103 mg, 791 μmol, 74% yield) as light-yellow crystals. ^{1}H NMR (500 MHz, CD_2Cl_2, ppm) δ = 8.07–8.04 (m, 2H, 2- and 6-C*H*), 7.27–7.20 (m, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, CD_2Cl_2, ppm): δ = 140.5 (2 C, 2- and 6-*C*H), 131.4 (2 C, 3- and 5-*C*H), 126.9 (4-C_q). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3081, 3023, 3000, 2987, 1472, 1445, 1242 (υ-N–O), 1187, 1113, 1040, 864 (υ-N–O), 827, 667, 517, 482. MS (EI, 70 eV) m/z (%) = 131 (35) [M with ^{37}Cl]$^+$, 129 (100) [M with ^{35}Cl]$^+$, 102 (10), 76 (10), 73 (23), 63 (18), 62 (11). HRMS (EI, [M]$^+$, C_5H_4ClNO) calcd.: 128.9982, found: 128.9981.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-DPJVRASYWY-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/DPJVRASYWYOFSJ-UHFFFAOYSA-N.1

4-Bromopyridine *N*-oxide (5a): 4-Nitropyridine *N*-oxide (2.50 g, 18.0 mmol, 1.00 equiv) was dissolved in acetic acid (35 mL), and acetyl bromide (32.9 g, 19.8 mL, 268 mmol, 15.0 equiv) was added dropwise at 25 °C. After stirring for 2.5 h at 80 °C, the reaction mixture was cooled to 21 °C. The crude product was added to crushed ice and then neutralized by adding aqueous 10 M NaOH. It was extracted with ethyl acetate and DCM. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was recrystallized from acetone twice to yield the title compound (1.97 g, 11.0 mmol, 64% yield) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$, $MeNO_2$, ppm): δ = 8.03–7.98 (m, 2H, 2- and 6-C*H*), 7.37–7.32 (m, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, $MeNO_2$, ppm): δ = 140.2 (2 C, 2- and 6-*C*H), 129.4 (2 C, 3- and 5-*C*H), 118.8 (4-C_q). ^{15}N NMR (50 MHz, $MeNO_2$, ppm): δ = –84.8 ppm (N^+-O^-). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3075, 3046, 3020, 2996, 2796, 2645, 1469, 1445, 1346, 1242(υ–N–O), 1208, 1187, 1126, 1094, 1037, 863 (υ–N–O), 839, 823, 696, 626, 514, 482. MS (EI, 70 eV) m/z (%) = 175 (100) [M with ^{81}Br]$^+$, 173 (100) [M with ^{79}Br]$^+$. HRMS (EI, [M]$^+$, C_5H_4BrNO) calcd.: 172.9476, found: 172.9475.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-ZRXLKDCFWJ-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/ZRXLKDCFWJECNO-UHFFFAOYSA-N.1

4,4′-Bipyridine-*N*-monoxide: 4-Bromopyridin-*N*-oxide (120 mg, 689 μmol, 1.00 equiv), pyridin-4-ylboronic acid (93.4 mg, 760 μmol, 1.10 equiv), potassium *tert*-butoxide (155 mg, 1.38 mmol, 2.00 equiv) and PEPPSI™-IPr catalyst (23.0 mg, 33.8 μmol, 0.0490 equiv) were combined with a degassed mixture of isopropanol (2.0 mL) and water (4.00 mL). After stirring for 10 minutes at 150 °C in a microwave reactor, the mixture was cooled to 21 °C, extracted with a mixture of chloroform and isopropanol (3:1) and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using a DCM/acetone (3:1) mixture with a 1% MeOH/NH_3 mixture (9:1) to yield the title compound (82.3 mg, 478 μmol, 69% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, $MeNO_2$ ppm) δ = 8.75–8.70 (m, 2H, 2- and 6-C*H*), 8.32–8.26 (m, 2H, 2′- and 6′-C*H*), 7.59–7.53 (m, 2H, 3′- and 5′-C*H*), 7.50–7.45 (m, 2H, 3- and 5-C*H*). ^{13}C NMR (126 MHz, DMSO-d6, ppm) δ = 151.0 (2 C, 2- and 6-*C*H), 143.4 (4-C_q), 139.9 (2 C, 2′- and 6′-*C*H), 135.3 (4′-C_q), 123.9 (2 C, 3′- and 5′-*C*H), 120.6 (2 C, 3- and 5-*C*H). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3210 (vw), 3081 (w), 3067 (w), 3031 (w), 1591 (m), 1561 (w), 1513 (w), 1477 (s), 1451 (w), 1408 (m), 1255 (vs), 1231 (vs), 1187 (vs), 1143 (w), 1102 (w), 1069 (w), 1023 (s), 990 (w), 866 (w), 850 (m), 840 (m), 812 (vs), 756 (w), 748 (w), 732 (w), 710 (m), 671 (w), 653 (w), 574 (vs), 489 (s). MS (EI, 70 eV) m/z (%) = 173.1 (12%) [M + H]$^+$, 172.1 (100%) [M]$^+$, 156.1 (28%) [M−O]$^+$, 155.1 (12%). HRMS (EI, [M]$^+$, $C_{10}H_8ON_2$) calcd.: 172.0637, found: 172.0637.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-JDNWJNJHGZ-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/JDNWJNJHGZHYNE-UHFFFAOYSA-N.1

2′-Fluoro-4,4′-bipyridine-*N*-monoxide: 4-Bromopyridin-*N*-oxide (121 mg, 697 μmol, 1.00 equiv), (2-fluoranylpyridin-4-yl)boronic acid (107 mg, 759 μmol, 1.09 equiv), potassium *tert*-butoxide (155 mg, 1.38 mmol, 1.98 equiv) and PEPPSI™-IPr catalyst (23.2 mg, 34.0 μmol, 0.0489 equiv) were combined with a degassed mixture of isopropanol (2.0 mL) and water (4.00 mL). After stirring for 10 minutes at 100 °C in a microwave reactor, the mixture was cooled to 21 °C, extracted with a mixture of chloroform and isopropanol (3:1) and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM/acetone/MeOH/NH_3 mixture (150:50:9:1) and recrystallized from toluene to yield the title compound (85.8 mg, 451 μmol, 65% yield) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.33 (d, J = 5.3 Hz, 1H, 6′-CH), 8.31–8.27 (m, 2H, 2- and 6-C*H*), 7.60–7.50 (m, 2H, 3- and 5-C*H*), 7.38 (dt, *J* = 5.3, 1.6 Hz, 1H, 5′-CH), 7.14–7.08 (m, 1H, 3′-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 164.7 (d, *J* = 239.5 Hz, 2′-*C*F), 148.9 (d, *J* = 8.2 Hz, 4′-Cq), 149.1 (d, J = 15.5 Hz, 6′-*C*H), 140.0 (2 C, 2- and 6-*C*H), 133.9 (d, J = 3.7 Hz, 4-C_q) 124.1 (2 C, 3- and 5-*C*H), 118.6 (d, *J* = 4.3 Hz, 5′-*C*H), 106.7 (d, *J* = 39.0 Hz, 3′-*C*H). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3105 (w), 3078 (w), 3053 (w), 3050 (w), 2961 (w), 2931 (w), 2856 (w), 1619 (s), 1608 (m), 1565 (w), 1537 (w), 1504 (s), 1469 (vs), 1449 (w), 1401 (vs), 1269 (s), 1241 (vs), 1203 (vs), 1184 (vs), 1109 (s), 1058 (s), 1034 (s), 996 (m), 899 (s), 884 (m), 860 (w), 832 (vs), 758 (w), 722 (m), 703 (m), 681 (m), 664 (m), 628 (m), 582 (vs), 558 (vs), 535 (s), 530 (s), 503 (s), 459 (vs), 439 (s). MS (EI, 70 eV) m/z (%) = 192.1 (12%) [M + 2H]$^+$, 191.1 (13%) [M + H]$^+$, 190.1 (100%) [M]$^+$, 174.1 (8%) [M−O]$^+$, 173.1 (7%) [M−OH]+, 134.1 (19%). HRMS (EI, [M]$^+$, $C_{10}H_7ON_2F$) calcd.: 190.0542, found: 190.0541.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-UTLTZGFWIC-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/UTLTZGFWICKPCV-UHFFFAOYSA-N.1

2′,6′-Difluoro-4,4′-bipyridine-*N*-monoxide: 4-Bromopyridin-*N*-oxide (121 mg, 697 μmol, 1.00 equiv), (2,6-difluoropyridin-4-yl)boronic acid (228 mg, 1.44 mmol, 2.06 equiv), potassium *tert*-butoxide (161 mg, 1.44 mmol, 2.06 equiv) and PEPPSI™-IPr catalyst (39.2 mg, 57.5 μmol, 0.0825 equiv) were combined with a degassed mixture of isopropanol (2.0 mL) and water (4.00 mL). After stirring for 10 minutes at 80 °C in a microwave reactor, the mixture was cooled to 21 °C, extracted with a mixture of chloroform and isopropanol (3 : 1) and washed with water and brine. The combined organic phase was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. The obtained crude product was purified via flash-chromatography on silica gel using DCM with a 1% MeOH/NH_3 mixture (9 : 1) to yield the title compound (17.6 mg, 84.5 μmol, 12% yield) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ = 8.34–8.28 (m, 2H, 2- and 6-C*H*), 7.56–7.52 (m, 2H, 3- and 5-C*H*), 7.02 (s, 2H, 3′- and 5′-C*H*). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ = 162.8 (dd, J = 247.6, 16.2 Hz, 2 C, 2′- and 6′-CF), 153.2 (t, J = 8.1 Hz, 4-C_q), 140.2 (2 C, 2-CH, and 6-CH), 132.7 (t, J = 3.6 Hz, 4′-C_q), 124.1 (m, 2 C, 3- and 5- C*H*), 104.4–102.8 (m, 2 C, 3′- and 5′- C*H*). ^{19}F NMR (471 MHz, $CDCl_3$, ppm) δ = -66.2 (2′- and 6′-C*F*). IR (ATR, cm^{-1}) $\tilde{\nu}$ = 3108 (w), 3074 (w), 3046 (w), 3013 (w), 2948 (w), 2932 (w), 1615 (vs), 1568 (m), 1547 (w), 1527 (w), 1502 (vs), 1455 (s), 1407 (vs), 1360 (m), 1265 (vs), 1214 (vs), 1179 (vs), 1139 (m), 1108 (m), 1075 (m), 1031 (vs), 1027 (s), 997 (m), 943 (w), 892 (w), 880 (s), 836 (vs), 745 (w), 724 (w), 662 (w), 630 (w), 609 (vs), 547 (vs), 510 (vs), 477 (m), 439 (w), 409 (w), 397 (w), 381 (w). MS (EI, 70 eV) m/z (%) = 269 (22), 219 (31), 208 (100), 181 (28), 169 (39), 152 (30), 131 (29), 119 (33), 69 (91). HRMS (EI, $[M]^+$, $C_{10}H_6F_2N_2O$) calcd.: 208.0443, found: 208.0444.

Additional information on the chemical synthesis is available via the Chemotion repository:

https://dx.doi.org/10.14272/reaction/SA-FUHFF-UHFFFADPSC-PZWQFNGKVR-UHFFFADPSC-NUHFF-NUHFF-NUHFF-ZZZ

Additional information on the analysis of the target compound is available via the Chemotion repository:

https://dx.doi.org/10.14272/PZWQFNGKVRXNMY-UHFFFAOYSA-N.1

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Modular synthesis · Building–blocks strategy · Non-centrosymmetric 4,4′-bipyridines · Molecular Tectonics · Pyridine N-oxidation · Palladium catalysis

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